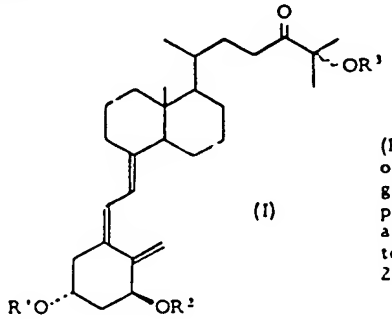
50771 D/28 B05 (B01) TEIJ 26.10.79 *JS 6061-351

TEIJIN KK

26.10.79-JP-137771 (26.05.81) A61k-31/59 C07c-172

1-Alpha, 25-dihydroxy-24-oxocholecalciferol derivs - exhibit vitamin/D 3 pharmacological activities, prepd. from 24-oxo-cholesta-5,7-diene cpds.

1α,25-Dihydroxy-24-oxocholecalciferols of formula (I) are new:



(I)

(R', R² and R³ = H or hydroxy protecting gp. (pref. 1-12C aliphatic or aromatic acyl, trialkylsilyl, 2-tetrahydropyranyl, or 2-tetrahydrofuranyl)).

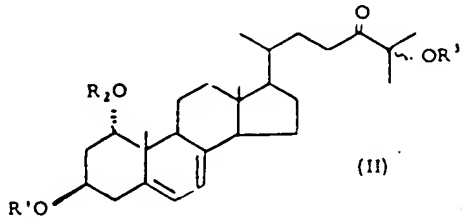
B(1-D2, 3-G). 2 109

USE/ADVANTAGE

(I) exhibit vitamin D_3-like pharmacological activities. On reduction of the 24-oxo, (I) are converted into 1α, 24, 25-trihydroxyvitamin D_3 as active vitamin D_3.

PREPARATION

(I) are prepd. by irradiating 1α,25-dihydroxy-24-oxocholesta-5,7-dienes (II) with ultraviolet rays to yield 1α,25-dihydroxy-24-oxoprevitamins D_3, isomerising the latter with thermal energy, if required followed by removal of the hydroxy protecting gp.



(II)

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The UV rays pref. have wavelength 200-360 nm, esp. 260-310 nm. The reaction is conducted in an inert solvent - including hydrocarbons and halohydrocarbons (e.g. hexane, heptane, PhH, PhMe, xylene, PhCl), ethers (e.g. Et_2O, THF, dioxane), and alcohols (e.g. MeOH, EtOH, PrOH) at a temp. of -20°C to 120°C, pref. -10°C to 50°C. The susbsequent thermal isomerisation is carried out at 20-120°C, pref. 40-100°C in the inert solvent.

EXAMPLE

A soln. of 70 mg 1α,3β,25-trihydroxy-24-oxocholesta-5,7-diene dissolved in a mixt. of 50 mg deoxygenated EtOH and 500 ml Et_2O was irradiated with a 200W lamp surrounded by a Vycor filter at 10-20°C with stirring for 6 hrs. The cold soln. was evapd. in vacuo at 30°C, and the residue was dissolved in 250 ml deoxygenated PhH and refluxed under heating for 2.5 hr. After the reaction completion, the mixt. was evapd. in vacuo, and the resulting residue was chromatographed on a thin layer of silica gel preliminarily treated with 2% $AgNO_3$-MeCN (solvent:$CHCl_3$-MeOH) and of silica gel ($PhH-Me_2CO$) to give 10.8 mg 1α,25-dihydroxy-24-oxovitamin D_3, mp. 91-93.5°C.(6ppW52)

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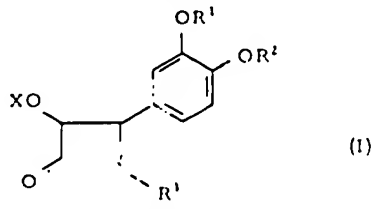
50772 D/28 B03 SAGA 24.10.79 *JS 6061-352

SAGAMI CHEM RES CENTRE

24.10.79-JP-135485 (26.05.81) C07c-101/77 C07d-205/08

3-Hydroxy-beta-lactam cpds. can be prepd. economically - and are used in DOPA prepn. used in antiparkinson treatment.

3-Hydroxy-β-lactam cpds. of formula (I) are new:



(I)

(R^1 and R^2 = H, lower alkyl, benzyl or acyl, or R^1 and R^2 taken together may form alkylene;
R^3 = alkyl, aryl or heteroaromatic gp.;
X = H, benzyl or tosyl).

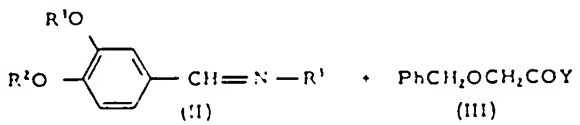
USE/ADVANTAGE

(I) can be converted into DOPA (useful as antiparkinson-

B(6-A2, 7-D1). 2 110

ism agent) on reaction with NaN_3, cleavage of the β-lactam ring, and acid treatment. (I) can be prepd. from cheap raw material.

PREPARATION



(II) (III)

step (A) → (I) (X = benzyl) step (B) → (I) (X = H)

step (C) → (I) (X = tosyl)

(Y is not defined but probably halogen).

Step (A) is carried out in a solvent, e.g. PhH, PhMe, THF, CH_2Cl_2, in presence of a tert. amine, e.g. Et_3N, Pr_3N, Bu_3N, pyridine, N-methylpiperidine, N-methylpyrrolidine DBU, at -78°C to 100°C.

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Step (B) comprises hydrogenolysis with Pd catalyst (e.g. Pd black, Pd-C) in a solvent (e.g. MeOH, EtOH, CH_2Cl_2, $CHCl_3$, PhH, PhMe, THF, MeCN, DMF) at room temp. to 150°C, pref. 50-100°C.

Step (C) comprises tosylation with p-TsCl in presence of a tert-amine in an aprotic solvent (e.g. CH_2Cl_2, $CHCl_3$, PhH, PhMe, THF, MeCN, Me_2CO, DMF, DMSO) at -30°C to 100°C.

EXAMPLE

To a soln. of 5.00 g 3,4-dimethoxybenzylideneaniline and 2.50 g Et_3N in 50 ml PhH was dropwise added slowly a soln. of 4.60 g benzyloxyacetyl chloride in 50 ml PhH under ice cooling. The reaction mixt. was gradually warmed up to room temp., stirred for 15 hrs., washed with water, dried on $MgSO_4$, and evapd. in vacuo to give 8.18 g light yellow oil. This was chromatographed on silica gel and eluted with n-hexane-EtOAc (4 : 1) to give 4.16 g cis-isomer of 1-phenyl-3-benzyloxy-4-(3,4-dimethoxyphenyl)azetidin-2-one as white crystals, m. pt. 130-133°C, and 2.38 g trans-isomer as a colourless oil, $n_D^{26.0}$: 1.6018.(10ppW52).

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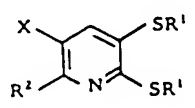
50774 D/28 B03 C02 E13 MITU 23.10.79

MITSUBISHI CHEM IND KK *J56061-354

23.10.79-JP-136740 (26.05.81) C07d-211/90 C07d-213/80

Nicotinic acid derivs. - used as agrochemicals, drugs and chemical intermediates

Nicotinic acid derivs. of formula (I) are new



(I)

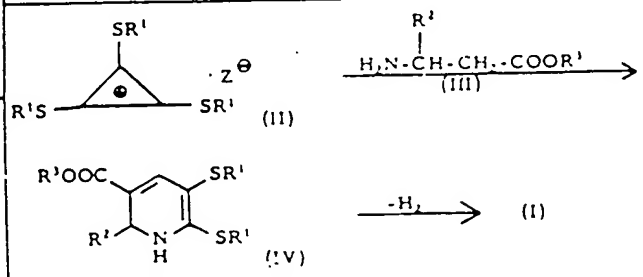
(R^1 = lower alkyl (e.g. Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, s-Bu, t-Bu);
R^2 = H, lower alkyl or aryl (e.g. phenyl, tolyl);
X = lower alkoxycarbonyl (e.g. MeOCO-, EtOCO-, n-PrOCO-, i-PrOCO-) or COOH).

USE

(I) are utilized as agrochemicals or drugs or as raw material in production of various chemicals. (I) can be converted into nicotinic acid or its esters by removal of $-SR^1$ on hydrogenolysis with Raney Ni catalyst.

PREPARATION

BC(7-D4) E(7-D4) N(5-A).



(II) (III) (IV) (I)

(Z^- = anion (e.g. halogen ion, ClO_4^-, BF_4^-, SbF_6^-, $SbCl_6^-$, $AlCl_4^-$);
R^3 = lower alkyl).

DETAILS

(II) has been described in J48096564.

The reaction is carried out in a solvent, e.g. CH_2Cl_2, $CHCl_3$, dimethoxyethane, DMF, MeOH, pref. in presence of a base, e.g. NaH, t-BuOK, at -100°C to the reflux temp. of

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the solvent used, pref. room temp. to 100°C, for a period of 0.1-10 hrs., pref. 0.5-5 hrs.

The subsequent dehydration is achieved by allowing (IV) to stand in a halogenohydrocarbon solvent, e.g. $CHCl_3$, CCl_4, fluorohydrocarbon, perfluorohydrocarbon, at 0°C to the reflux temp. of the solvent used, pref. room temp., for a period of 3-24 hrs., pref. 10-15 hrs.

EXAMPLE

A mixt. of tri-t-butylthiocyclopropenium perchlorate (1 mmole, 403 mg.) and methyl 2-aminopropionate (2 mmole) in 40 ml. DMF is allowed to stand at 80°C in presence of NaH (3 mmole) for 1 hr. Water is added, and the mixt. is extracted with hexane. The extract is dried on Na_2SO_4 and evapd., the residue is chromatographed on silica gel to give methyl 2,3-di-t-butylthio-1,6-dihydronicotinate in 72% yield.

This is dissolved in 10 ml. CCl_4 and allowed to stand under air for 24 hrs. to give methyl 2,3-di-t-butylthionicotinate in quantitative yield.(5ppW52)

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